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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,697	05/05/2005	Mark E. Dudley	233876	9619

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,697	DUDLEY ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 11/19/07 is acknowledged.

Claims 1-40 are pending.

Claims 1-22 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

2. Claims 23-40 read on a method of promoting the regression of a cancer in a mammal comprising administering nonmyeloablative lymphodepleting chemotherapy and subsequently administering autologous T-cells , which have been previously isolated and stimulated in vitro with the antigen of the cancer of are under consideration in the instant application.

3. It is noted that the specification and instant claims have been amended to include the amino acid sequences of MART-1 and gp 100 peptides, which sequences are incorporated into the specification by references to Kawakami et al and Dudley et al., accordingly. The instant application at pages 1 and 9 has a specific identification of the referenced publication and direction to the specific portion of the referenced document where the subject matter being incorporated may be found. In re de Seversky , 474 F.2d 671, 177 USPQ 144, (CCPA 1973).

However, the amendment **must be accompanied by an affidavit or declaration** executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In view of the amendment, filed 11/19/07 the following new rejections are set forth below

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 23- 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2002, Vol. 25, IDS) or WO'03/004625 (IDS) each in view of Seiter et al. (J of Immunology, 2002, V.25, pages 252-263, IDS) and newly cited Riddell et al (J Immunol. Method, 1990, 128, pages 189-201) for the same reasons set forth in the previous Office Action, mailed on 08/20/07.

Applicant's arguments, 11/19/07 have been fully considered, but have not been found convincing

Applicant asserts that as supported by the Declaration under 37 CFR 1.131 by Dr. Dudley, the invention of the instant specification was conceive of and reduced to practice before July 2, 2001.

This is not found convincing because the Dudley's Declaration is deficient for following reasons:

(i) A declaration under 37 C.F.R. § 1.131 that is signed by the inventive entity must be signed by ***all*** inventors of the claimed subject matter. In this case, the inventive entity of the instant application includes 3 inventors and yet only one of them (Dr. Dudley) has signed the declaration.

(ii) The declaration ***fails to establish possession of the whole scope of the invention*** (such as new limitations added into the amended claims) in the sense that the claim as a whole reads on it. See M.P.E.P. § 715.02.

Dudley et al., teach a method of promoting the regression of a cancer in a mammal comprising administering non-myeloablative lymphodepleting chemotherapy and subsequently administering autologous T-cells , which have been previously isolated and stimulated *in vitro* with the antigen of the cancer (see entire document, Abstract in particular). Dudley et al., teach that non-myeloablating treatment comprises administering of cyclophosphamide (60 mg/kg) and fludarabine (25 mg/m^2) are administered intravenously (see page 244 in particular). Dudley et al., teach administration of IL-2 by intravenous injection (see Materials and Method in particular).

WO'625 teaches a method of promoting the regression of a cancer in a mammal comprising administering non-myeloablative lymphodepleting chemotherapy and subsequently administering autologous T-cells , which have been previously isolated and stimulated *in vitro* with the antigen of the cancer (see entire document, pages 5, 14, 15 and overlapping pages 17-18 in particular) in particular). WO' 625 teaches that a therapeutic effective amount of purified T cell that can vary from $5x10^6$/kg to $1x10^8$ /kg (see page 13 and 19 in particular). WO' 625 teaches administering of various T cell growth factor, including IL-2, that can promote growth and activation of the autologous T cell (see pages 14 and 16 in particular).

Dudley et al., and WO' 625 do not explicitly teach a method of promoting the regression of a cancer in a mammalian wherein T cells which have been previously isolated and stimulated *in vitro* with the antigen of the cancer have been further subjected to one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2 and wherein antigen of cancer consists of amino acids 26-35 of MART-1 or amino acids 209-217 of gp100, as claimed in claims 36, 39 and 40.

Seiter et al., teach melanoma differentiated antigens MART-1 and gp100 that are frequently observed as a targets of tumor infiltrating lymphocytes (see entire document, Abstract in particular). Seiter et al., teaches that peptides consisting of amino acids 25-35 of MART-1 and amino acids 209-217 of gp100 has been used for in-vitro sensitization of T cells (see Material and Methods in particular). Seiter et al., teaches that incubation of T cells with said antigens consistently increase reactivity of T cells towards said immunodominant epitope. Obtaining said melanoma-specific T cells would be beneficiary for treating and promoting regression of melanoma in patients.

Newly cited Riddell et al., teach a method of *iv vitro* growing and expanding a large number of antigen specific T cells comprising rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching Seiter et al., and Riddell et al., to those of Dudley et al., and WO' 625 to obtain a claimed a method of promoting the regression of a cancer in a mammalian wherein antigen of cancer consists of amino acids 26-35 of MART-1 or amino acids 209-217 of gp100.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

All the claimed elements were known in the prior art and one skill in the art could have combine the elements as claimed by known methods with no change in their respective function and the combination would have yield predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc.*, 550U.S.-, 82 USPQ2d 1385, 2007).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. Claims 23- 35,37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2001, Vol. 24, IDS) or WO'9705239 in view of US Patent 6,447,767 (IDS) and newly cited Riddell et al. for the same reasons set forth in the previous Office Action, mailed on 08/20/07.

Applicant's arguments, 11/19/07 have been fully considered, but have not been found convincing

Applicant asserts that as supported by the Declaration under 37 CFR 1.131 by Dr. Dudley, the invention of the instant specification was conceive of and reduced to practice before July 2, 2001.

This is not found convincing because the Dudley's Declaration is deficient for following reasons:

(i) A declaration under 37 C.F.R. § 1.131 that is signed by the inventive entity must be signed by ***all*** inventors of the claimed subject matter. In this case, the inventive entity of the instant application includes 3 inventors and yet only one of them (Dr. Dudley) has signed the declaration.

(ii) The declaration ***fails to establish possession of the whole scope of the invention*** (such as new limitations added into the amended claims) in the sense that the claim as a whole reads on it. See M.P.E.P. § 715.02.

Dudley et al., teach a method of promoting the regression of melanoma in a mammal which comprising administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro (see entire document, Abstract and page 364 in particular). Dudley et al teach that to same patient IL-2 at various dosages (125,000 IU/kg -and 720,000IU/kg) was administered subsequently to autologous T cells (see Material and methods in particular). Dudley et al teach that some patien had also received the MART-1 peptide (see page 364 in particular). Dudley et al. teach that to overcome the poor persistence of adoptive transferred of T cells several variation on patient treatment protocol could be considered, including lymphodepleting chemotherapy. Dudley et al. teach that said treatment might improve lymphocyte survival and treatment efficacy.

WO' 239 teaches a method of promoting the regression of cancer in a mammal compring administering to mammal an autologous T-cells which have been stimulated *in vitro* with antigen of the cancer (see entire document, Abstract and pages 12, 17, 22, 48 and 49 in particular). WO' 239 teaches the administration of IL-2 to the same patients at various concentrations (see pages 16 and 18 in particular)

The claimed invention differs from the reference teaching in that the Dudley et al., or WO' 239 does not explicitly teach a patient treatment protocol comprising administering non-myeloablative lymphodepleting chemotherapy comprising administration of cyclophosphamide and fludarabine prior to administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro and wherein said T cells which have been previously isolated and stimulated *in vitro* with the antigen of the cancer have been further subjected to one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2 .

US Patent '767 teaches a method of treating cancer patient, including melanoma, comprising administering to the patient non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior of administering T cells (see entire document, Abstract, columns 3, 4 , 8 and 9 in particular). US Patent '767 teaches that said non-myeloablative treatment should be used to overcome the poor persistence of adoptive transferred of T cells.

Newly cited Riddell et al., teach a method of *iv vitro* growing and expanding a large number of antigen specific T cells comprising rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '767 and Riddell et al., to those of Dudley et al., or WO'239 to obtain a claimed method of promoting the regression of cancer in a mammal comprising administering non-myeloablative lymphodepleting chemotherapy comprising administration of cyclophosphamide and fludarabine prior to administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because to overcome the poor persistence of adoptive transferred of T cells several variation on patient treatment protocol could be considered, including non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior of administering T cells as taught by US Patent '767 that can be used in combination with by the method taught by Dudley et al. or WO'239. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Claims 26 –34 are included because it would be conventional and within the skill of the art to : (i) determine the optimal duration and dosage of administering cyclophosphamide and fludarabine; or (ii) optimal amount of administered T cells. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Claims 36 39 and 40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2001, Vol. 24, IDS) or WO'9705239 in view of US Patent 6,447,767 (IDS) and Riddel et al., as applied to claims 23- 35, 37 and 38 above, and further in view of in view of Seiter et al. (J of Immunology, 2002, V.25, pages 252-263, IDS) for the same reasons set forth in the previous Office Action, mailed on 08/20/07.

Applicant's arguments, 11/19/07 have been fully considered, but have not been found convincing

Applicant asserts that as supported by the Declaration under 37 CFR 1.131 by Dr. Dudley, the invention of the instant specification was conceive of and reduced to practice before July 2, 2001.

This is not found convincing because the Dudley's Declaration is deficient for following reasons:

(i) A declaration under 37 C.F.R. § 1.131 that is signed by the inventive entity must be signed by ***all*** inventors of the claimed subject matter. In this case, the inventive entity of the instant application includes 3 inventors and yet only one of them (Dr. Dudley) has signed the declaration.

(ii) The declaration ***fails to establish possession of the whole scope of the invention*** (such as new limitations added into the amended claims) in the sense that the claim as a whole reads on it. See M.P.E.P. § 715.02.

The teaching of Dudley et al., WO' 239 and US Patent'767 and Riddell et al., have been discussed, supra.

Dudley et al., WO' 625 and US Patent '767 and Riddel et al., do not explicitly teach a method of promoting the regression of a cancer in a mammalian wherein antigen of cancer consists of amino acids 26-35 of MART-1 or amino acids 209-217 of gp100, as claimed in claims 36, 39 and 40.

Seiter et al., teach melanoma differentiated antigens MART-1 and gp100 that are frequently observed as a targets of tumor infiltrating lymphocytes (see entire document, Abstract in particular). Seiter et al., teaches that peptides consisting of amino acids 25-35 of MART-1 and amino acids 209-217 of gp100 has been used for in-vitro sensitization of T cells (see Materials and Methods in particular). Seiter et al., teaches that incubation of T cells with said antigens consistently increase reactivity of T cells towards said immunodominant epitope. Obtaining said melanoma-specific T cells would be beneficiary for treating and promoting regression of melanoma in patients

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching Seiter et al., to those of Dudley et al., WO' 625 and US Patent '767 to obtain a claimed a method of promoting the regression of a cancer in a mammalian wherein antigen of cancer consists of amino acids 26-35 of MART-1 or amino acids 209-217 of gp100.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

All the claimed elements were known in the prior art and one skill in the art could have combine the elements as claimed by known methods with no change in their respective function and the combination would have yield predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc.*, 550U.S.-, 82 USPQ2d 1385, 2007).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571/ 272-0878.
The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PRIMARY EXAMINER

1/31/08